

PRESCRIBING INFORMATION: MABTHERA® (rituximab) Please refer to MabThera SPC for

full prescribing information **Indications:** Treatment of CD20-positive diffuse large B-cell non-Hodgkin's lymphoma (DLBCL) in combination with CHOP. Treatment of follicular lymphoma (FL) (i) with chemotherapy in previously untreated patients with stage III-IV FL, (ii) as maintenance therapy in patients with relapsed/refractory FL responding to induction therapy with chemotherapy with or without MabThera, (iii) in patients with stage III-IV FL who are chemo-resistant or in second or subsequent relapse after chemotherapy. First-line treatment of patients with chronic lymphocytic leukaemia (CLL) in combination with chemotherapy.

Dosage and Administration: Administer prepared MabThera as IV infusion through a dedicated line, with full resuscitation facilities immediately available and under supervision of an experienced physician. Do not administer as IV push or bolus. Administer premedication (eg an anti-pyretic and an antihistamine) before each infusion. Consider premedication with glucocorticoids, if not given in combination with a glucocorticoid-containing chemotherapy. Monitor closely for onset of cytokine release syndrome (CRS). Severe reactions e.g. severe dyspnoea, bronchospasm or hypoxia require immediate interruption of infusion. Only restart infusion if symptoms resolve, at half previous rate. *Diffuse large B-cell non-Hodgkin's lymphoma:* In combination with CHOP, 375mg/m² on day 1 of each chemotherapy cycle for 8 cycles, after the glucocorticoid component of CHOP. *Follicular lymphoma:* (i) In combination with chemotherapy, 375mg/m² on day 1 of each chemotherapy cycle for up to 8 cycles, after the glucocorticoid component if it is part of the chemotherapy regimen, (ii) As maintenance in patients responding to induction therapy, 375mg/m² once every 3 months until disease progression or for maximum 2 years (iii) Induction as a single agent (includes retreatment) following relapse, 375mg/m² once weekly for four weeks. *Chronic lymphocytic leukaemia:* In combination with chemotherapy 375 mg/m² administered on day 1 of the first treatment cycle followed by 500 mg/m² administered on day 1 of each subsequent cycle for 6 cycles in total. Chemotherapy to be given after MabThera infusion. Prophylaxis with adequate hydration and administration of uricostatics starting 48 hours prior to start of therapy is recommended for CLL patients to reduce the risk of tumour lysis syndrome. For CLL patients whose lymphocyte counts are > 25 x 10⁹/L it is recommended to administer prednisone/prednisolone 100 mg intravenous shortly before infusion with MabThera to decrease the rate and severity of acute infusion reactions and/or cytokine release syndrome.

First Infusion: Recommended initial rate is 50mg/hr; after the first 30 minutes increase by 50mg/hr every 30 minutes to maximum of 400 mg/hr. *Subsequent Infusions:* Initial rate 100mg/hr; increase by 100mg/hr every 30 minutes to a maximum of 400mg/hr. *Dose adjustments:* No dose reductions of MabThera recommended. Apply standard dose reductions to chemotherapy agents

in combination with MabThera. MabThera is not recommended in children. **Contra-indications:** Hypersensitivity to any component of this product or to murine proteins. **Precautions:** Use extreme caution and closely monitor first infusion when treating patients with $\geq 25 \times 10^9/l$ circulating malignant cells or high tumour burden (higher risk of severe cytokine release syndrome (CRS)). Consider reduced rate for first infusion or a split dosing over two days during the first cycle. Severe CRS: may be associated with some features of tumour lysis syndrome e.g. hyperuricaemia, hyperkalaemia, hypocalcaemia, hypophosphataemia, acute renal failure, elevated LDH and may be associated with acute respiratory failure and death. If severe CRS manifests stop infusion immediately and start aggressive symptomatic treatment. See SPC for full details. Anaphylaxis and other hypersensitivity reactions have been reported following IV administration of proteins to patients. Hypotension may occur during MabThera infusion; consider withholding anti-hypertensive medications 12 hours prior to infusion. Caution in patients with a history of pulmonary insufficiency, those with pulmonary tumour infiltration and patients with history of cardiac disease and/or cardiotoxic chemotherapy. Experience in patients with neutrophils $< 1.5 \times 10^9/l$ and/or platelet counts $< 75 \times 10^9/l$ is limited therefore use caution. Do regular full blood counts (FBC) when MabThera is given in combination with chemotherapy; consider periodic FBC during monotherapy. MabThera should not be administered to patients with an active and/or severe infection (e.g. tuberculosis, sepsis and opportunistic infections). Carefully monitor patients with history of hepatitis B infection for active infection when MabThera is used with chemotherapy. Consider differential diagnosis of Progressive Multifocal Leucoencephalopathy (PML) in patients reporting neurological symptoms. Safety or efficacy of immunization with any vaccine has not been studied. **Drug interactions:** Limited data available on possible drug interactions with MabThera. Patients with human antimouse antibody/human anti-chimeric antibody (HAMA/HACA) titres may have allergic or hypersensitivity reactions when treated with other monoclonal antibodies. **Pregnancy and lactation:** No adequate data from use in pregnant women. Do not give MabThera to a pregnant woman unless the potential benefit outweighs the risk. May cause B-cell depletion in the foetus. Effective contraception required in women of childbearing age during and for up to 12 months following MabThera therapy. Women should not breastfeed during, and for 12 months following, MabThera therapy. **Undesirable effects:** Monotherapy: *Common adverse reactions:* Infusion related effects, observed in over 50% of patients on monotherapy, predominantly during first infusion, usually in first 2 hours; mainly fever, chills and rigors; other symptoms include flushing, angioedema, nausea, urticaria/rash, fatigue, headache, throat irritation, rhinitis, vomiting and tumour pain; accompanied by hypotension and bronchospasm in about 10% of cases. Incidence of infusion related reactions

decreases substantially with subsequent infusions. Infections: B-cell depletion occurs in 70-80% of patients but decreased serum immunoglobulins in only a minority of patients; bacterial, viral & fungal infections, including severe infections and sepsis, were reported in single-arm trials.

Haematological adverse events: occurred in a minority of patients and usually mild and reversible. Severe (grade 3 and 4) events occurred: thrombocytopenia, neutropenia, severe anaemia, haemolytic anaemia, pure red cell aplasia. Cardiovascular events: exacerbation of pre-existing cardiac conditions such as angina pectoris, myocardial infarction, hypotension, hypertension, arrhythmia. Bulky disease: higher incidence of grade 3 and 4 adverse events. Serum sickness reported.

When used in combination with chemotherapy: Similar adverse reactions occur as for monotherapy. In addition: DLBCL: Grade 3/4 adverse events, including grade 2 infections, reported at a $\geq 2\%$ higher incidence with R-CHOP compared to CHOP alone were: bronchitis, herpes zoster, sinusitis, dyspnoea, shivering, hypertension, atrial fibrillation. FL: Grade 3/4 adverse events reported at a $\geq 2\%$ higher incidence with R-CVP compared to CVP alone or with R-CHOP compared to CHOP alone were fatigue and neutropenia, nausea, constipation, neutropenia, febrile neutropenia, alopecia, hypersensitivity. Maintenance therapy: Grade 3/4 adverse events reported at a $\geq 2\%$ higher incidence with maintenance therapy compared to observation were: respiratory tract infection, neutropenia, leucopenia, alopecia and cardiac disorders. CLL: overall incidence of grade 3/4 infections was comparable between the treatment groups (R-FC, FC).

Serious adverse reactions observed in post-marketing surveillance: Serious viral infection. Late neutropenia, pancytopenia, aplastic anaemia. Severe events in patients with prior cardiac condition or cardiotoxic chemotherapy, heart failure, myocardial infarction. Hearing loss. Severe vision loss. Multi-organ failure. Infusion related reactions, anaphylaxis, tumour lysis syndrome, cytokine release syndrome, serum sickness. Very rare cases of Hepatitis B reactivation, including fulminant hepatitis with fatal outcome. Progression of pre-existing Kaposi's sarcoma, mainly in patients with HIV. Cranial neuropathy, peripheral neuropathy, facial nerve palsy, loss of other senses. Renal failure. Bronchospasm, respiratory failure, pulmonary infiltrates, interstitial pneumonitis. Gastro-intestinal perforation. Severe bullous skin reactions, toxic epidermal necrolysis. Vasculitis (various types). *Prescribers should consult the SPC in relation to other side-effects.* **Legal Category:** POM. **Presentations:** 100mg of rituximab in 10ml (10mg/ml) pack of 2 vials. 500mg of rituximab in 50ml (10mg/ml) pack of 1 vial. **Marketing Authorisation**

Numbers: EU/1/98/067/001 (100mg). EU/1/98/067/002 (500mg). **Marketing Authorisation**

Holder: Roche Registration Limited, 6 Falcon Way, Welwyn Garden City, AL7 1TW. MABTHERA is a registered trade mark. **Date of Preparation:** March 16th 2009